SPECIFICATION AMENDMENTS:

To comply with the examiner's request the following changes are made to the specifications:

Page 1: in the section **technical field:**

This patent relates to novel compositions of matter containing optically pure enantiomers of ~~(S,S)-S-adenosylmethionine~~ S-adenosyl-l-methionine (SAM-e), defined non-racemic ratios of (S,S)-S-adenosyl-l-methionine to (R,S)-S-adenosyl-l-methionine, and to therapeutic uses of these new compositions. More particularly, the invention relates to the substantially optically pure enantiomer ~~(S,S)-S-adenosylmethionine~~ (S,S)-S-adenosyl-l-methionine, defined non-racemic ratios of (S,S)-S-adenosyl-l-methionine, pharmaceutically acceptable salts and pharmaceutical compositions that contain them as active principles.

Page 5: **second paragraph:**

~~Sam-e~~ SAM-e also attenuates the damage caused by tumor necrosis factor alpha and can also decrease the amount of tumor necrosis factor alpha secreted by cells.

Page 6: **second paragraph:**

SAM-e is commercially available using fermentation technologies that result in SAM-e formulations varying between 60 and 80 % purity. (That is, the final product contains 60-80% of the active or ~~(S, S)-SAM-e~~ (S,S)-S-adenosyl-l-methionine and 20-40% of the inactive or ~~(R, S)-SAM-e.)~~ (R,S)-S-adenosyl-l-methionine.) (Gross, A., Geresh, S., and Whitesides, Gm (1983) Appl. Biochem. Biotech. 8, 415.)

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N.E. not clear

Page 6: **3rd paragraph**

Segal and Eichler showed that the enzyme bound ~~(S,S) SAM e~~ (S,S)-S-adenosyl-l-methionine 10 fold more tightly than the biologically inactive ~~(R,S) SAM e~~ (R,S)-S-adenosyl-l-methionine thus

Page 7: **first paragraph**

Other methyltransferases have been reported to bind ~~(R,S) SAM e~~ (R,S)-S-adenosyl-l-methionine to the same extent as ~~(S,S) SAM e~~ (S,S)-S-adenosyl-l-methionine and thus ~~(R,S) SAM e~~ (R,S)-S-adenosyl-l-methionine could act as a competitive inhibitor of that enzyme.

Page 7: **second paragraph**

The present patent thus envisions the use of any of the salts of SAM-e already disclosed in the prior art to stabilize the enantiomeric forms of SAM-e. Examples of such salts disclosed in the prior art include the following: a lipophilic salt of S-adenosyl-l-methionine(SAM)-e of the formula SAM.sup.n+ [R—CO—NH—(CH.sub.2).sub.2 —SO.sup.-.sub.3].sub.n in which R-CO is a member selected from the group consisting of C.sub.12-C.sub.26 saturated and unsaturated, linear and branched acyl and C.sub.12 -C.sub.26 cycloalkyl-substituted acyl, and n is an integer from 3 to 6 according to the SAM charge ; double salts corresponding to the formula SAM.sup.+.HSO.sub.4.sup.-.H.sub.2 SO.sub.4 .2 CH.sub.3 C.sub.6 H.sub.4 SO.sub.3 H. ; salts (S, S) -s-adenosyl-l-methionine with sulphonic acids selected from the group consisting of methanesulphonic, ethanesulphonic, 1-n-dodecanesulphonic, 1-n-octadecanesulphonic, 2-chloroethanesulphonic, 2-bromoethanesulphonic, 2-hydroxyethanesulphonic, 3-hydroxypropanesulphonic, d-,1-,d,1-10-camphorsulphonic, d-,1-,d,1-3-bromocamphor-10-sulphonic, cysteic, benzenesulphonic,p-chlorobenzenesulphonic, 2-mesitylbenzenesulphonic, 4-biphenylsulphonic, 1-naphthalenesulphonic, 2-naphthalenesulphonic, 5-sulphosalicylic, p-acetylbenzenesulphonic, 1,2-

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ethanedisulphonic, methanesulphonic acid, ethanesulphonic acid, 1-n-dodecanesulphonic acid, 1-n-octadecanesulphonic acid, 2-chloroethanesulphonic acid, 2-bromoethanesulphonic acid,2-hydroxyethanesulphonic acid, d-,l-,d,l-10-camphorsulphonic acid, d-,l-,d,l-3-bromocamphor-10-sulphonic acid, cysteic acid , benzenesulphonic acid, 3-hydroxypropanesulphonic acid, 2-mesitylbenzenesulphonic acid, p-chlorobenzenesulphonic acid,4-biphenylsulphonic acid, 2-naphthalenesulphonic acid, 5-sulphosalicylic acid, 1,2-ethanedisulphonic acid, p-acetylbenzenesulphonic acid, 1-naphthalenesulphonic acid, o-benzenedisulphonic and chondroitinesulphuric acids, and double salts of said acids with sulphuric acid; S-adenosyl-L-methionine or a pharmaceutically acceptable salt thereof and an effective amount of a lithium salt selected from the group consisting of lithium chloride, lithium bromide, lithium iodide, lithium sulfate, lithium nitrate, lithium phosphate, lithium borate, lithium carbonate, lithium formate, lithium acetate, lithium citrate, lithium succinate and lithium benzoate; water-soluble salt of a bivalent or trivalent metal is a member selected from the group consisting of calcium chloride, ferric chloride, magnesium chloride, and magnesium sulfate; the salt of S-adenosyl-L-methionine is a member selected from the group consisting of salts of S-adenosyl-L-methionine with hydrochloric acid, sulfuric acid, phosphoric acid, formic acid, acetic acid, citric acid, tartaric acid, and maleic acid; and a double salt of S-adenosyl-L-methionine with said acids; a salt of S-adenosyl-l-methionine and a water-soluble polyanionic substance selected from the group consisting of a polyphosphate, metaphosphate, polystyrene sulfonate, polyvinyl sulfonate, polyvinyl sulfate, polyvinyl phosphate, and polyacrylate wherein the stoichiometric ratio of mols of S-adenosyl-l-methionine to gram-equivalent of the polyanionic substance is from 0.1:1 to 0.5; a salt of S-adenosyl-l-methionine wherein the polyanionic substance is a polyphosphate, para-polystyrene sulfonate or metaphosphate; a salt of the general formula: SAM-e.nR(O).sub.m (SO.sub.3 H)p (I) where m can be zero or 1; n is 1.5 when p is 2, and is 3 when p is 1; R is chosen from the group consisting of alkyl, phenylalkyl and carboxyalkyl, in which the linear or branched alkyl chain contains from 8 to 18 carbon atoms, and in particular for producing SAM-e salts of sulphonic acids, or of sulphuric acid esters, or of dioctylsulphosuccinic acid. However the more preferred salts of the S-adenosyl-l-methionine enantiomers are chosen from the group consisting of salts of S-adenosyl-l-

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methionine enantiomers with sulfuric acid, p-toluenesulfonic acid, 1,4-butanedisulphonic acid.

Page 7: **third paragraph**

United States Patent 2,969,353, Shunk et al, January 24, 1962, discloses a method for the preparation of ~~Sam-e~~ SAM-e and a stable salt of SAM-e but not the use of an optically pure enantiomer of SAM-e.

Page 9: **third paragraph**

Since the two enantiomeric forms of S-adenosyl-l-methionine do not exhibit the same biological activity but rather that the ~~(R,S) S-adenosyl-l-methionine~~ (R,S)-S-adenosyl-l-methionine enantiomer exhibits no biological activity (or even competitive inhibition), it is therefore necessary for a rational pharmaceutical therapy to use the more active enantiomeric form of S-adenosyl-l-methionine. In this regard, and in view of the ~~(R,S) SAM-e~~ (R,S)-S-adenosyl-l-methionine enantiomer to act as a competitive inhibitor of ~~(S,S) SAM-e~~ (S,S)-S-adenosyl-l-methionine in methyltransferase reactions, a more ideal SAM-e composition would be the substantially optically pure biologically active ~~(S,S) SAM-e~~ (S,S)-S-adenosyl-l-methionine form or a defined non-racemic ratio of (S,S)-S-adenosyl-l-methionine to (R,S)-S-adenosyl-l-methionine.

Page 10: **first paragraph**

It is an object of the present invention to provide new compositions of SAM-e containing substantially pure biologically active ~~(S,S) SAM-e~~ (S,S)-S-adenosyl-l-methionine or a defined non-racemic ratio of (S,S)-S-adenosyl-l-methionine to (R,S)-S-adenosyl-l-methionine.

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Page 10**: third paragraph**

Briefly stated, the present invention discloses compositions of substantially optically pure enantiomeric forms of SAM-e, defined non-racemic ratios of (S,S)-S-adenosyl-l-methionine to (R,S)-S-adenosyl-l-methionine, and methods for the use thereof.

Page 11: **second paragraph**

As mentioned above, this invention is generally directed to compositions of a substantially optically pure enantiomeric form of SAM-e salts or defined non-racemic ratios of (S,S)-S-adenosyl-l-methionine to (R,S)-S-adenosyl-l-methionine.

Page 12: **fourth paragraph**

In a preferred embodiment, the substantially optically pure enantiomeric forms of SAM-e salts of the present invention or a non-racemic mixture of (S,S)-S-adenosyl-l-methionine and (R,S)-S-adenosyl-l-methionine are administered to a warmblooded animal as a pharmaceutical, prophylactic or cosmetic composition containing at least one substantially optically pure enantiomeric forms of SAM-e salt or a non-racemic mixture of (S,S)-S-adenosyl-l-methionine and (R,S)-S-adenosyl-l-methionine in combination with at least one pharmaceutically, prophylactically or cosmetically acceptable carrier or diluent.

Page 13: **place at end of first paragraph:**

In another embodiment, a pharmaceutical composition of the non-racemic ratio of (S,S)-S-adenosyl-l-methionine to (R,S)-S-adenosyl-l-methionine is preferably from about 80.01% to about 100% of (S,S)-

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S-adenosyl-l-methionine to about 19.09% to about 0.0% by weight of (R,S)-S-adenosyl-l-methionine. In yet another embodiment, a pharmaceutical composition of the non-racemic ratio of (S,S)-S-adenosyl-l-methionine to (R,S)-S-adenosyl-l-methionine is more preferably from about 80.01% to about 96.09% of (S,S)-S-adenosyl-l-methionine to about 19.09% to about 3.01% by weight of (R,S)-S-adenosyl-l-methionine. In yet a further embodiment, a pharmaceutical composition of the non-racemic ratio of (S,S)-S-adenosyl-l-methionine to (R,S)-S-adenosyl-l-methionine is most preferably from about 80.01% to about 95% of (S,S)-S-adenosyl-l-methionine to about 19.09% to about 5% by weight of (R,S)-S-adenosyl-l-methionine.

Page 14: EXAMPLE 1

~~(S, S) s-adenosylmethionine~~ (S,S)-S-adenosyl-l-methionine was prepared according to the method of Hoffman (Hoffman, Chromatographic Analysis of the Chiral and Covalent Instability of S-adenosyl-l-methionine, Biochemistry 1986, 25 4444-4449).

~~(S, S) S-adenosylmethionine~~ (S,S)-S-adenosyl-l-methionine p-toluene sulfonate 400 mg was administered twice daily in an open, non-blind study of 10 volunteers who gave informed consent. All patients had normal results on pre-study medical examinations, including laboratory examinations. Patients received 400 mg of ~~(S, S) S-adenosylmethionine~~ (S,S)-S-adenosyl-l-methionine p-toluene sulfonate in an enteric-coated tablet form twice daily for 14 days or until remission of depression symptoms. The 10 patients satisfied the DSM-III criteria for a major depressive episode. Patients' symptoms were monitored daily using the Hamilton Rating Scale for Depression. 9 patients completed the study. (One patient declined to continue the study after beginning.) Eight of the nine patients who completed the trial improved over the 14 days. One patient had no change at all. No side effects were noted or reported by any of the patients nor as measured by laboratory or physical examination. ~~(S, S) S-adenos~~

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~~ylmethionine~~ (S,S)-S-adenosyl-l-methionine p-toluene sulfonate 400 mg twice daily appeared to be safe and effective in this small, non-blinded study of depression.